Functional connectivity changes during epileptogenesis: a longitudinal resting-state fMRI study

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Introduction

Temporal lobe epilepsy (TLE) is the most common form of epilepsy in adults. Research has shown that abnormal functional brain networks could be involved in the development of epilepsy and its comorbidities[1]. Gaining more insight into these networks can be useful for the development of new therapies. Resting state-functional MRI can visualize changes in functional networks on a whole-brain level[2]. In this study, we aim to map changes in functional networks during epileptogenesis in the intraperitoneal kainic acid (IPKA) rat model for TLE using longitudinal resting-state fMRI and graph theory.

Subjects and Methods

Twenty-four adult male Sprague-Dawley rats (276±15g) were used in this study. Seventeen animals were intraperitoneally injected with kainic acid (KA) according to the protocol of Hellier et al.[3] resulting in status epilepticus (SE). The other 7 animals were injected with saline and used as a control group. Rs-fMRI images were acquired before and at 5 time points during the development of epilepsy on a 7T system, while the animals were anesthetized with medetomidine. The images were preprocessed using SPM12. The Pearson correlation coefficient was calculated between the fMRI time series of 38 regions of interest (ROIs) and stored in a correlation matrix. Several network measures were calculated using a graph theoretical network analysis toolbox (GRETNA)[4], and plotted as a function of time.

Results and Discussion

In Fig. 1 the distribution of the correlation coefficients is shown at different time points during the development of epilepsy in the IPKA rat model and in control animals. The correlation coefficients shift to smaller values during epileptogenesis and their distribution becomes wider. This indicates that network connections progressively become weaker during the development of epilepsy. Four network measures can be seen in Fig. 2: clustering coefficient, local efficiency, characteristic path length and global efficiency. In Fig. 2A and 2B clustering coefficient and local efficiency are shown. Both decrease during epileptogenesis, indicating a decrease in segregation or local interconnectivity in the functional brain network. Fig. 2C and 2D show that characteristic path length increases and global efficiency decreases during epileptogenesis. This indicates that the integration in the brain network decreases, so there is a decrease in overall communication efficiency.

Conclusion

The results of this study show that functional brain network connections progressively become weaker and that segregation and integration of the network are decreased during epileptogenesis. In the next phase of this study, EEG monitoring will be used to characterize the severity of epilepsy in these rats to investigate how changes in functional brain networks during epileptogenesis correlate with epilepsy severity.

References

1. Chiang, S. & Haneef, Z. Graph theory findings in the pathophysiology of temporal lobe epilepsy. *Clin. Neurophysiol.* **125,** 1295–1305 (2014).

2. Hutchison, R. M., Mirsattari, S. M., Jones, C. K., Gati, J. S. & Leung, L. S. Functional Networks in the Anesthetized Rat Brain Revealed by Independent Component Analysis of Resting-State fMRI. *J. Neurophysiol.* **103,** (2010).

3. Hellier, J. L., Patrylo, P. R., Buckmaster, P. S. & Dudek, F. E. Recurrent spontaneous motor seizures after repeated low-dose systemic treatment with kainate: assessment of a rat model of temporal lobe epilepsy. *Epilepsy Res.* **31,** 73–84 (1998).

4. Wang, J. *et al.* GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. *Front. Hum. Neurosci.* **9,** 386 (2015).

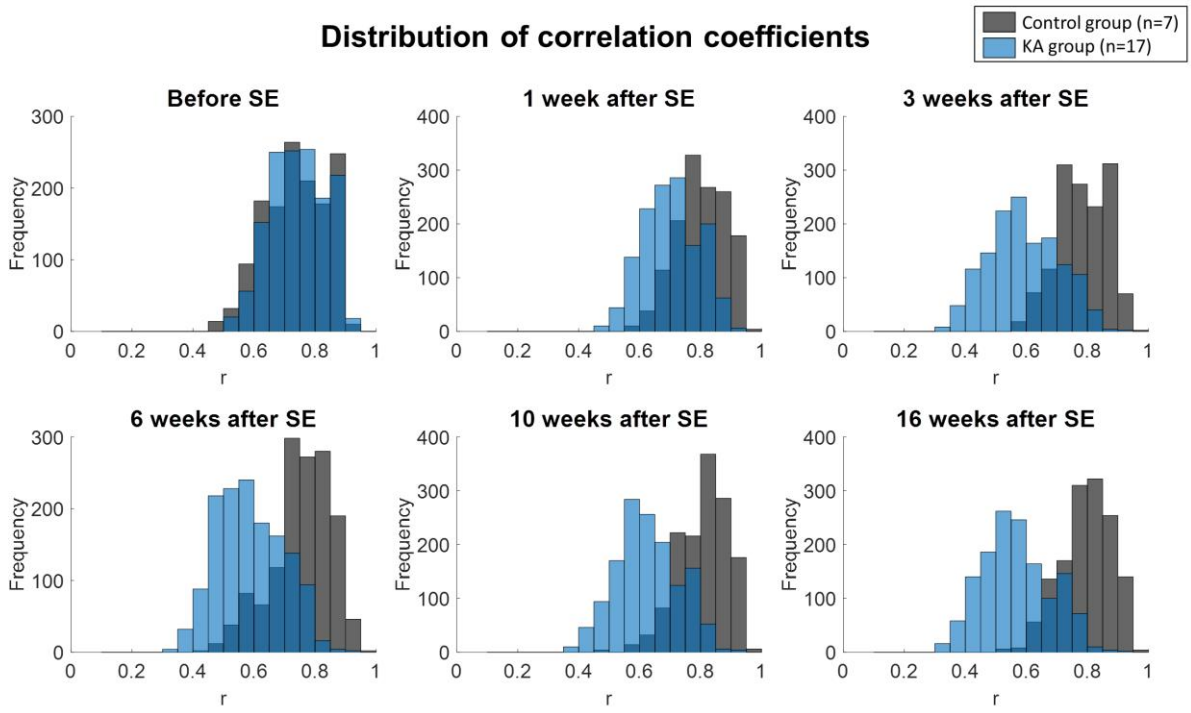

Fig. 1. Distribution of correlation coefficients during epileptogenesis in IPKA animals and control animals

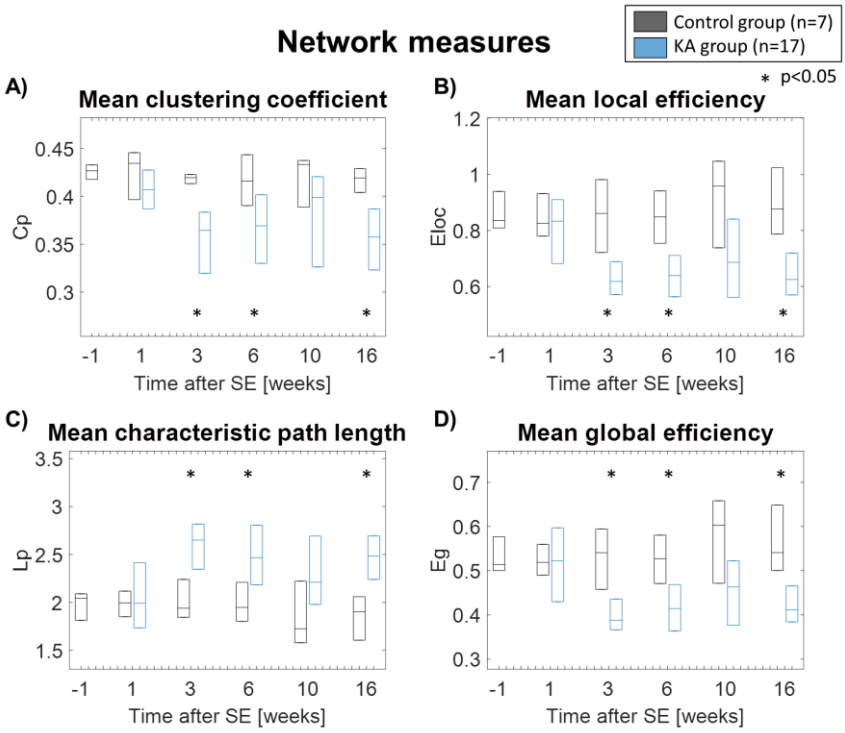

Fig. 2. Changes in network measures during epileptogenesis: A) Mean clustering coefficient, B) Mean local efficiency, C) Mean characteristic path length, D) Mean global efficiency